PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Long-term mortality of patients ablated for atrial fibrillation: a retrospective, population-based epidemiological study in Apulia, Italy
AUTHORS	Di Monaco, Antonio; Vitulano, Nicola; Troisi, Federica; Quadrini, Federico; Guida, Piero; Grimaldi, Massimo

VERSION 1 – REVIEW

REVIEWER	Poppe, K University of Auckland, biostats
REVIEW RETURNED	07-Dec-2021

GENERAL COMMENTS	The authors compare survival in people who have received an AF ablation to that of people in the general population (which would include a mixture of all chronic diseases). The method and analysis are clearly conveyed. a) The Introduction includes a lot of information about AF in general, yet this study is specifically about mortality after AF ablation so it is confusing to describe the longitudinal effects of non-ablated AF in any detail. I suggest that much of paragraph 2 can be removed, and it can be picked up towards the bottom of page 4 when ablation starts to be talked about. b) The Discussion is similarly a lot longer than it needs to be. There are good clear points about the findings of this study and how they add to the existing body of knowledge, but they and the findings of other studies get repeated. This is a simple analysis with clear findings and the Discussion would benefit from editing. I'd suggest the content and message can be conveyed in half the number of words. c) Page 8 row 60 – "Evidence of AF beneficial impact on death…" suggest intended to say " Evidence of beneficial impact of AF ablation on death…" ?

REVIEWER	タカダ, ミドリ Osaka Center for Cancer and Cardiovascular Disease Prevention
REVIEW RETURNED	28-Dec-2021

GENERAL COMMENTS	1. General comments This article tells us that the long-term mortality of patients who underwent catheter ablation of AF is the same as that of the general population in the Puglia region. While this finding was interesting, the results might not be generalizable to other settings or areas, as participants were patients of the single hospital (unknown hospital size) and the choice of the standard/reference population from the limited region for calculating SMR seems to reduce the external

	validity of this study. In addition, although previous studies have not given expected mortality in the general population and SMR in the articles, the long-term mortality of patients ablated for atrial fibrillation has been reported in the past, with or without HF, and the novelty and originality of the study are considered to be modest. Furthermore, the review of previous studies and the description of methods, results, and Tables in the manuscript seem not to be detailed. 2. Specific comments a) Major i) p5, line 40-: Please describe the data collection, the eligibility criteria, and the methods of selection of participants in detail. How did the authors diagnose AF, define patients with drug-refractory AF and HF, completely detect HF at baseline and during follow-up among all of the participants, and deal with the missing data and loss to follow-up such as emigrants? ii) p5, line 17- : The authors stated, “data on long-term risk after catheter ablation of AF are lacking.” However, several studies have reported the long-term (assumed median/mean several-year follow-up period similar to this study) mortality of patients ablated for atrial fibrillation, with or without HF. Although these previous studies did not show expected mortality in the general population and SMR in the articles probably due to the different purpose of study from this study, literature-reviews of them are more informative. To the best of my knowledge, there have been studies that examined the long-term mortality of patients ablated for atrial fibrillation (Saglietto et al., 2020. doi: 10.1111/jce.14429., Samuel et al., 2020. doi: 10.1093/europace/euaa036., Srivatsa et al., 2018. doi: 10.1161/CIRCEP.117.005739., Jarman et al., 2017. doi: 10.2147/POR.S134777., Friberg et al., 2016. doi: 10.1093/eurheartj/ehw087., Nademanee et al., 2015. doi: 10.1016/j.hrthm.2014.09.049., and Bunch et al., 2011. doi: 10.1111/j.1540-8167.2011.02035.x.). There have also been studies that reported the long-term mortality of patients ablated for atrial fibrillation with HF (Marrouche et al., 2018. doi: 10.1056/NEJMoa1707855. , Luigi et al., 2016. doi: 10.1161/CIRCULATIONAHA.115.019406., and Bunch et al., 2015. doi: 10.1111/jce.12602.). iii) p5, line 59: The authors stated, “The expected numbers of deaths were derived using mortality rates from the general population of Puglia Region..”. In previous studies (Friberg L, et al. 2007. doi: 10.1093/eurheartj/ehm308., Potpara, et al., 2010. doi: 10.2298/vsp1002132p., Olsson, et al., 2013. doi: 10.1016/j.ijcard.2013.10.028., Fored, et al., 2008. doi: 10.1093/europace/eun118.), it seems typical to use national data as the general population for calculating the SMR, probably because they thought that the expected number of deaths would be more accurate among a larger population. The use of only the residents of Puglia Region as the general population may have limited the generalizability of the results of this study. Was there any specific reason why the author used such an approach? In addition, when the investigators assess excess mortality using the SMR, they usually assume that the expected mortality rate in the general population reflects the rate that would occur in unexposed persons, but it is almost inevitably biased in that all general populations contain exposed individuals (Jones, et al. 1998. doi: 10.1093/oxfordjournals.aje.a009567.). Were there any efforts to

	address this potential bias. Or is there a special setting in the Puglia region where all catheter ablations for AF are performed in the author's hospital so that the general population in Puglia region can be regarded as an unexposed population? b) Minor i) p4, line 24-: The authors stated “AF may lead to a decrease in ejection fraction….” and “Progressive heart muscle disease is …”. The authors should cite the appropriate articles that support these statements. ii) p5, line 45: The authors should clarify the current guidelines referred to in this statement. iii) p6, line 10: The authors stated, “We used the Student's t-test to compare patients’ age between groups.” Which groups did the authors compared? Why did the author compare only age? Where are these results in the manuscript and Tables? iv) p6, line 12: The authors stated “Mortality over time was evaluated using Kaplan-Meier curves that were compared with the Log-Rank test”. Please describe which groups you compared the mortality rates between. v) p6, line 35: The authors stated, “Patients aged <55 years were 368 (29.2%) while 453 (36.0%) were in the range 55-65 and 439 (34.8%) were older than 65.” Please indicate where this statement corresponds to in Table 1. vi) p6, line 40: Please describe the participants’ characteristics shown in Table 1 in detail. vii) p6, line 56: The authors stated, “Table 2 shows detailed outcome data during follow-up.”. Please do not abbreviate "detailed outcome data", but specify what Table 2 shows. vii) p7, line 10: The authors stated, “Age was not related to an excess of mortality than the general population (Table 2).”. Please provide specific figures in the text. viii) p7, line 47: The authors stated, “Second, mortality after AF ablation was significantly increased in subjects with a pre-existing history of HF and in those with a diagnosis made during follow-up.” However, the authors cannot attribute causality from the observed associations between HF and mortality after AF ablation due to the nature of this study design. I recommend that the authors tone down their statements by using other words such as “higher”. ix) p8, line 59: The authors stated, “Evidence of AF beneficial impact on death is lacking.”. However, one of the previous studies showed a remarkably favorable prognosis of patients with persistent AF was found both in comparison with the general population and in comparison with patients having other types of AF (Friberg L, et al. 2007. doi: 10.1093/eurheartj/ehm308.). x) p17, Table 1: I recommend that you present patient characteristics by analysis group (no heart failure, with heart failure at baseline, new onset of heart failure during follow-up)×presence/absence of death. This information is helpful for readers to understand the difference of patents’ characteristics

	between groups. xi) p18, Table 2: Please provide a concrete title that describes the information in table 2 instead of “Outcome during follow-up”. It might be helpful to refer to the title of Table 2 in one of the previous studies (Friberg L, et al. 2007. doi: 10.1093/eurheartj/ehm308.). You should clarify in the footnote that the new onset of heart failure during follow-up is 1119 people without heart failure at baseline. xii) p21, Figure 2: Figure 2 shows the same SMRs as in Table 2, except for 95% confidence intervals. Therefore, I recommend to summarize the results of Figure 2 in Table 2.

VERSION 1 – AUTHOR RESPONSE

Response to reviewer 1

We are very grateful to the reviewer for attention and helpful comments to our manuscript, which helped to improve our work considerably.

The authors compare survival in people who have received an AF ablation to that of people in the general population (which would include a mixture of all chronic diseases). The method and analysis are clearly conveyed.

a) The Introduction includes a lot of information about AF in general, yet this study is specifically about mortality after AF ablation so it is confusing to describe the longitudinal effects of non-ablated AF in any detail. I suggest that much of paragraph 2 can be removed, and it can be picked up towards the bottom of page 4 when ablation starts to be talked about.

R. Dear reviewer, as suggested we modified the introduction.

b) The Discussion is similarly a lot longer than it needs to be. There are good clear points about the findings of this study and how they add to the existing body of knowledge, but they and the findings of other studies get repeated. This is a simple analysis with clear findings and the Discussion would benefit from editing. I’d suggest the content and message can be conveyed in half the number of words.

R. Dear reviewer, as suggested we modified the discussion.

c) Page 8 row 60 – “Evidence of AF beneficial impact on death…” suggest intended to say “ Evidence of beneficial impact of AF ablation on death…” ?

R. We modified the sentence as suggested

Response to reviewer 2

We are very grateful to the reviewer for attention and helpful comments to our manuscript, which helped to improve our work considerably.1. General comments

This article tells us that the long-term mortality of patients who underwent catheter ablation of AF is the same as that of the general population in the Puglia region. While this finding was interesting, the results might not be generalizable to other settings or areas, as participants were patients of the single hospital (unknown hospital size) and the choice of the

standard/reference population from the limited region for calculating SMR seems to reduce the external validity of this study. In addition, although previous studies have not given expected mortality in the general population and SMR in the articles, the long-term mortality of patients ablated for atrial fibrillation has been reported in the past, with or without HF, and the novelty and originality of the study are considered to be modest. Furthermore, the review of previous studies and the description of methods, results, and Tables in the manuscript seem not to be detailed.

2. Specific comments

a) Major

i) p5, line 40-: Please describe the data collection, the eligibility criteria, and the methods of selection of participants in detail. How did the authors diagnose AF, define patients with drug-refractory AF and HF, completely detect HF at baseline and during follow-up among all of the participants, and deal with the missing data and loss to follow-up such as emigrants?

R. Dear reviewer, we improved the manuscript as suggested. In particular, data were derived from the Cardiac Interventional Registry implemented at our hospital; vital status and dates of death were obtained for residents in Puglia by using regional Health Information System and AF/ HF were defined following the European Society of Cardiology guidelines (page 5 ; row 8). We have no missing data and we included only patients resident in Puglia.

ii) p5, line 17- : The authors stated, "data on long-term risk after catheter ablation of AF are lacking." However, several studies have reported the long-term (assumed median/mean several-year follow-up period similar to this study) mortality of patients ablated for atrial fibrillation, with or without HF. Although these previous studies did not show expected mortality in the general population and SMR in the articles probably due to the different purpose of study from this study, literature-reviews of them are more informative. To the best of my knowledge, there have been studies that examined the long-term mortality of patients ablated for atrial fibrillation (Saglietto et al., 2020. doi: 10.1111/jce.14429., Samuel et al., 2020. doi: 10.1093/europace/euaa036., Srivatsa et al., 2018. doi: 10.1161/CIRCEP.117.005739., Jarman et al., 2017. doi: 10.2147/POR.S134777., Friberg et al., 2016. doi: 10.1093/eurheartj/ehw087., Nademanee et al., 2015. doi: 10.1016/j.hrthm.2014.09.049., and Bunch et al., 2011. doi: 10.1111/j.1540-8167.2011.02035.x.). There have also been studies that reported the long-term mortality of patients ablated for atrial fibrillation with HF (Marrouche et al., 2018. doi: 10.1056/NEJMoa1707855. , Luigi et al., 2016. doi: 10.1161/CIRCULATIONAHA.115.019406., and Bunch et al., 2015. doi: 10.1111/jce.12602.).

R. Dear reviewer, we agree with you regarding the sentence. The aim of this study is to compare mortality after catheter ablation of AF compared to general population. AS you suggested, we modified the sentence reporting :"Although AF is significantly associated with mortality and morbidity, data on long-term risk after catheter ablation of AF compared with the general population is not well characterized and the dynamic of this relative risk is uncertain in terms patient's age and underlying risk profile"

iii) p5, line 59: The authors stated, "The expected numbers of deaths were derived using mortality rates from the general population of Puglia Region..". In previous studies (Friberg L, et al. 2007. doi: 10.1093/eurheartj/ehm308., Potpara, et al., 2010. doi: 10.2298/vsp1002132p., Olsson, et al., 2013. doi: 10.1016/j.ijcard.2013.10.028., Fored, et al., 2008. doi: 10.1093/europace/eun118.), it seems typical to use national data as the general population for

calculating the SMR, probably because they thought that the expected number of deaths would be more accurate among a larger population. The use of only the residents of Puglia Region as the general population may have limited the generalizability of the results of this study. Was there any specific reason why the author used such an approach?

R. Dear reviewer, as suggested we reported data of Italian general population (see table 3, methods and and results). In particular, when observed mortality was compared to Italian general population, all results were confirmed.

In addition, when the investigators assess excess mortality using the SMR, they usually assume that the expected mortality rate in the general population reflects the rate that would occur in unexposed persons, but it is almost inevitably biased in that all general populations contain exposed individuals (Jones, et al. 1998. doi: 10.1093/oxfordjournals.aje.a009567.). Were there any efforts to address this potential bias. Or is there a special setting in the Puglia region where all catheter ablations for AF are performed in the author's hospital so that the general population in Puglia region can be regarded as an unexposed population?

R. Dear reviewer, we agree with your comment. However, in the general population the percentage of patients who undergo ablation of AF is very low (<1%) and the bias is porbably not significant

b) Minor

i) p4, line 24-: The authors stated "AF may lead to a decrease in ejection fraction…." and "Progressive heart muscle disease is …". The authors should cite the appropriate articles that support these statements.

R. Dear reviewer, as requested by other reviewers we removed this paraghraph

ii) p5, line 45: The authors should clarify the current guidelines referred to in this statement.

R. Dear reviewer, as suggested we reported the guidelines (see methods)

iii) p6, line 10: The authors stated, "We used the Student's t-test to compare patients' age between groups." Which groups did the authors compared? Why did the author compare only age? Where are these results in the manuscript and Tables?

R. Dear reviewer, as suggested we improved the paragraph regarding the statistical analyses.

iv) p6, line 12: The authors stated "Mortality over time was evaluated using Kaplan-Meier curves that were compared with the Log-Rank test". Please describe which groups you compared the mortality rates between.

R. Dear reviewer, as suggested we improved the paragraph regarding the statistical analyses.

v) p6, line 35: The authors stated, "Patients aged <55 years were 368 (29.2%) while 453 (36.0%) were in the range 55-65 and 439 (34.8%) were older than 65." Please indicate where this statement corresponds to in Table 1.

R. Dear reviewer, we improved the table 1 as suggested.

vi) p6, line 40: Please describe the participants' characteristics shown in Table 1 in detail.

R. Dear reviewer, we reported the participants' characteristics as requested (see results)

vii) p6, line 56: The authors stated, "Table 2 shows detailed outcome data during follow-up.". Please do not abbreviate "detailed outcome data", but specify what Table 2 shows.

R. Dear reviewer, we modified the data as requested

vii) p7, line 10: The authors stated, "Age was not related to an excess of mortality than the general population (Table 2).". Please provide specific figures in the text.

R. Dear reviewer, we modified the text as requested (see table 3 and figure 2)

viii) p7, line 47: The authors stated, "Second, mortality after AF ablation was significantly increased in subjects with a pre-existing history of HF and in those with a diagnosis made during follow-up." However, the authors cannot attribute causality from the observed associations between HF and mortality after AF ablation due to the nature of this study design. I recommend that the authors tone down their statements by using other words such as "higher".

R. Dear reviewer, we agree wit your comment. We modified the sentence (page 8; rows 4-5)

ix) p8, line 59: The authors stated, "Evidence of AF beneficial impact on death is lacking.". However, one of the previous studies showed a remarkably favorable prognosis of patients with persistent AF was found both in comparison with the general population and in comparison with patients having other types of AF (Friberg L, et al. 2007. doi: 10.1093/eurheartj/ehm308.).

R. Dear reviewer, the article reported data regarding AF and not catheter ablation of AF. The aim of our study is to investigate mortality after catheter ablation of AF compared to general population.

x) p17, Table 1: I recommend that you present patient characteristics by analysis group (no heart failure, with heart failure at baseline, new onset of heart failure during follow-up)×presence/absence of death. This information is helpful for readers to understand the difference of patents' characteristics between groups.

R. Dear reviewer, as suggested we modified table 1 and 2.

xi) p18, Table 2: Please provide a concrete title that describes the information in table 2 instead of "Outcome during follow-up". It might be helpful to refer to the title of Table 2 in one of the previous studies (Friberg L, et al. 2007. doi: 10.1093/eurheartj/ehm308.). You should clarify in the footnote that the new onset of heart failure during follow-up is 1119 people without heart failure at baseline.

R. Dear reviewer, as suggested we modified the title as "Mortality and expected risk during follow-up with standardized mortality ratios in relation to age categories, history of heart failure and development of heart failure." WE added your suggestion regarding people without HF at baseline

xii) p21, Figure 2: Figure 2 shows the same SMRs as in Table 2, except for 95% confidence intervals. Therefore, I recommend to summarize the results of Figure 2 in Table 2.

R. Dear reviewer, as suggested we modified table 2 and figure 2

VERSION 2 – REVIEW

REVIEWER	Poppe, K University of Auckland, biostats
REVIEW RETURNED	06-Feb-2022

GENERAL COMMENTS	The methods section notes that written informed consent was obtained however was this study approved by an ethics board?

REVIEWER	タカダ, ミドリ Osaka Center for Cancer and Cardiovascular Disease Prevention
REVIEW RETURNED	12-Feb-2022

GENERAL COMMENTS	Comments on the response Dear authors, thank you for working on the revision of the manuscript. However, the manuscript seems to has room for improvement. a) Major i) p5, line 40-: Please describe the data collection, the eligibility criteria, and the methods of selection of participants in detail. How did the authors diagnose AF, define patients with drug-refractory AF and HF, completely detect HF at baseline and during follow-up among all of the participants, and deal with the missing data and loss to follow-up such as emigrants? R. Dear reviewer, we improved the manuscript as suggested. In particular, data were derived from the Cardiac Interventional Registry implemented at our hospital; vital status and dates of death were obtained for residents in Puglia by using regional Health Information System and AF/ HF were defined following the European Society of Cardiology guidelines (page 5 ; row 8). We have no missing data and we included only patients resident in Puglia. Comment on R to Major i). 1. Thank you for your response. It seems to be hard to understand the background of the study population only from the sentence “the Cardiac Interventional Registry implemented at your hospital.” Could the authors cite the profile paper of this registry at the authors’ hospital? If there is no profile paper, I would like the authors to explain from when until when this registry was conducted and what patients were registered in this registry in the manuscript. 2. If it is applicable, I would like the authors to clearly in the manuscript that AF in this study indicates clinical AF in the ESC guideline (not including AHRE nor subclinical AF), and all cases of AF were diagnosed by ECG at the registration. 3. I suggest the authors explain the definition of drug-refractory AF in this study. For example, the authors defined patients who did not respond to the treatment after using at least X (one, two, three)

	types of AAD for Y months and more as drug-refractory AF, and so on. 4. I would like the authors to explain in the manuscript how the authors detect each HF (history of HF at the baseline and new onset of HF during the follow-up). In particular, for the new onset of HF during the follow-up, I wonder if the authors could specify what algorithm the authors followed and what examination (type of examination and cut-off) the authors used to diagnose the new onset of HF. 5. It would be great if the authors could present a flow chart in the manuscript that showed the inclusion and exclusion criteria and the number of the study population. ii) p5, line 17- : The authors stated, “data on long-term risk after catheter ablation of AF are lacking.” However, several studies have reported the long-term (assumed median/mean several-year follow-up period similar to this study) mortality of patients ablated for atrial fibrillation, with or without HF. Although these previous studies did not show expected mortality in the general population and SMR in the articles probably due to the different purpose of study from this study, literature-reviews of them are more informative. To the best of my knowledge, there have been studies that examined the long-term mortality of patients ablated for atrial fibrillation (Saglietto et al., 2020. doi: 10.1111/jce.14429., Samuel et al., 2020. doi: 10.1093/europace/euaa036., Srivatsa et al., 2018. doi: 10.1161/CIRCEP.117.005739., Jarman et al., 2017. doi: 10.2147/POR.S134777., Friberg et al., 2016. doi: 10.1093/eurheartj/ehw087., Nademanee et al., 2015. doi: 10.1016/j.hrthm.2014.09.049., and Bunch et al., 2011. doi: 10.1111/j.1540-8167.2011.02035.x.). There have also been studies that reported the long-term mortality of patients ablated for atrial fibrillation with HF (Marrouche et al., 2018. doi: 10.1056/NEJMoa1707855. , Luigi et al., 2016. doi: 10.1161/CIRCULATIONAHA.115.019406., and Bunch et al., 2015. doi: 10.1111/jce.12602.). R. Dear reviewer, we agree with you regarding the sentence. The aim of this study is to compare mortality after catheter ablation of AF compared to general population. AS you suggested, we modified the sentence reporting :”Although AF is significantly associated with mortality and morbidity, data on long-term risk after catheter ablation of AF compared with the general population is not well characterized and the dynamic of this relative risk is uncertain in terms patient’s age and underlying risk profile” Comment on R to Major ii). Thank you for modifying the sentence. To make the sentence more specific and more concise, how would you like to revise the sentence as follows? from “Although AF is significantly associated with mortality and morbidity, …, especially, presence or occurrence of HF.” (pages 4-5, lines 56-60 and 1-6) to “Although data on long-term risks after catheter ablation of AF with or without HF has been identified (citation XXX), those compared with the general population are not well characterized”. iii) p5, line 59: The authors stated, “The expected numbers of deaths were derived using mortality rates from the general population of Puglia Region..”. In previous studies (Friberg L, et al. 2007. doi:

	10.1093/eurheartj/ehm308., Potpara, et al., 2010. doi: 10.2298/vsp1002132p., Olsson, et al., 2013. doi: 10.1016/j.ijcard.2013.10.028., Fored, et al., 2008. doi: 10.1093/europace/eun118.), it seems typical to use national data as the general population for calculating the SMR, probably because they thought that the expected number of deaths would be more accurate among a larger population. The use of only the residents of Puglia Region as the general population may have limited the generalizability of the results of this study. Was there any specific reason why the author used such an approach? R. Dear reviewer, as suggested we reported data of Italian general population (see table 3, methods and and results). In particular, when observed mortality was compared to Italian general population, all results were confirmed. Comment on R to Major iii). The word “confirmed” seems to make the sentence in the manuscript vague. I would appreciate it if the authors could modify this sentence as follows, “When observed mortality was compared to Italian general population, all results were similar to the results in Puglia (Table 3).” iv) In addition, when the investigators assess excess mortality using the SMR, they usually assume that the expected mortality rate in the general population reflects the rate that would occur in unexposed persons, but it is almost inevitably biased in that all general populations contain exposed individuals (Jones, et al. 1998. doi: 10.1093/oxfordjournals.aje.a009567.). Were there any efforts to address this potential bias. Or is there a special setting in the Puglia region where all catheter ablations for AF are performed in the author's hospital so that the general population in Puglia region can be regarded as an unexposed population? R. Dear reviewer, we agree with your comment. However, in the general population the percentage of patients who undergo ablation of AF is very low (<1%) and the bias is porbably not significant Comment on R to Major iv). Thank you for the response. I was satisfied with your reply. b) Minor i) p4, line 24-: The authors stated “AF may lead to a decrease in ejection fraction….” and “Progressive heart muscle disease is …”. The authors should cite the appropriate articles that support these statements. R. Dear reviewer, as requested by other reviewers we removed this paraghraph Comment on R to Minor i). Thank you for the modification. I understand. ii) p5, line 45: The authors should clarify the current guidelines referred to in this statement. R. Dear reviewer, as suggested we reported the guidelines (see methods) Comment on R to Minor ii). Thank you for citing. iii) p6, line 10: The authors stated, “We used the Student's t-test to compare patients’ age between groups.” Which groups did the authors compared? Why did the author compare only age? Where are these results in the manuscript and Tables?

	R. Dear reviewer, as suggested we improved the paragraph regarding the statistical analyses. Comment on R to Minor iii). Thank you for the improvement. iv) p6, line 12: The authors stated “Mortality over time was evaluated using Kaplan-Meier curves that were compared with the Log-Rank test”. Please describe which groups you compared the mortality rates between. R. Dear reviewer, as suggested we improved the paragraph regarding the statistical analyses. Comment on R to Minor iv). Thank you for the response. I was satisfied with your improvement in the sentence. v) p6, line 35: The authors stated, “Patients aged <55 years were 368 (29.2%) while 453 (36.0%) were in the range 55-65 and 439 (34.8%) were older than 65.” Please indicate where this statement corresponds to in Table 1. R. Dear reviewer, we improved the table 1 as suggested. Comment on R to Minor v). I was not able to find the improvement the authors mentioned. Could it be that the numerical values in this sentence do not need to be shown in Table 1? vi) p6, line 40: Please describe the participants’ characteristics shown in Table 1 in detail. R. Dear reviewer, we reported the participants’ characteristics as requested (see results) Comment on R to Minor vi). I believe that the word “higher/lower” is more appropriate to describe the participants' characteristics in the manuscript than the word “associated”. This is because what the authors did in Table 1 was to compare the participants’ characteristics across groups (presence/absence of HF), not to examine the association between participants’ characteristics and presence/absence of HF. For example, how would like you to state as follows? “The prevalence of hypertension, A, B and C (patients’ characteristics) were higher/lower among those with the participants with HF (group) than among those without HF” vii) p6, line 56: The authors stated, “Table 2 shows detailed outcome data during follow-up.” Please do not abbreviate "detailed outcome data", but specify what Table 2 shows. R. Dear reviewer, we modified the data as requested Comment on R to Minor vii). Thank you for the response. I was satisfied with your modification. vii) p7, line 10: The authors stated, “Age was not related to an excess of mortality than the general population (Table 2).”. Please provide specific figures in the text. R. Dear reviewer, we modified the text as requested (see table 3 and figure 2) Comment on R to Minor vii). Thank you for the response. I was satisfied with your modification. viii) p7, line 47: The authors stated, “Second, mortality after AF ablation was significantly increased in subjects with a pre-existing

	history of HF and in those with a diagnosis made during follow-up." However, the authors cannot attribute causality from the observed associations between HF and mortality after AF ablation due to the nature of this study design. I recommend that the authors tone down their statements by using other words such as "higher". R. Dear reviewer, we agree wit your comment. We modified the sentence (page 8; rows 4-5) Comment on R to Minor viii). Thank you for the response. I was satisfied with your modification. ix) p8, line 59: The authors stated, "Evidence of AF beneficial impact on death is lacking.". However, one of the previous studies showed a remarkably favorable prognosis of patients with persistent AF was found both in comparison with the general population and in comparison with patients having other types of AF (Friberg L, et al. 2007. doi: 10.1093/eurheartj/ehm308.). R. Dear reviewer, the article reported data regarding AF and not catheter ablation of AF. The aim of our study is to investigate mortality after catheter ablation of AF compared to general population. Comment on R to Minor ix). Thank you for your reply. Certainly. x) p17, Table 1: I recommend that you present patient characteristics by analysis group (no heart failure, with heart failure at baseline, new onset of heart failure during follow-up)×presence/absence of death. This information is helpful for readers to understand the difference of patents' characteristics between groups. R. Dear reviewer, as suggested we modified table 1 and 2. Comment on R to Minor x). Thank you for the response. However, my comment may have been a little unclear and did not convey my intention to the author. I apologize for it. In order to deal with this comment, how would you like to summarize the current Tables 1 and 2 into Table 1 that shows participants' characteristics referring to the attached Excel? In addition, I recommend that the authors reconsider the statistical analyses in this section. I believe that a chi-square test and ANOVA would be more appropriate than Cox proportional hazard model. This is because what the authors should do in this section is to compare the characteristics of the participants across the groups used in the main analysis. The authors need not compare the survival times between groups. xi) p18, Table 2: Please provide a concrete title that describes the information in table 2 instead of "Outcome during follow-up". It might be helpful to refer to the title of Table 2 in one of the previous studies (Friberg L, et al. 2007. doi: 10.1093/eurheartj/ehm308.). You should clarify in the footnote that the new onset of heart failure during follow-up is 1119 people without heart failure at baseline. R. Dear reviewer, as suggested we modified the title as "Mortality and expected risk during follow-up with standardized mortality ratios in relation to age categories, history of heart failure and development of heart failure." WE added your suggestion regarding people without HF at baseline Comment on R to Minor xi). Thank you for the response. I was satisfied with your modification.

	xii) p21, Figure 2: Figure 2 shows the same SMRs as in Table 2, except for 95% confidence intervals. Therefore, I recommend to summarize the results of Figure 2 in Table 2. R. Dear reviewer, as suggested we modified table 2 and figure 2 Comment on R to Minor xii). Thank you for the response. I was satisfied with your modification.

VERSION 2 – AUTHOR RESPONSE

Response to reviewer 2:

We are very grateful to the reviewer for his/her attention and helpful comments to our manuscript, which helped to improve our work considerably.

a) Major

i) p5, line 40-: Please describe the data collection, the eligibility criteria, and the methods of selection of participants in detail. How did the authors diagnose AF, define patients with drug-refractory AF and HF, completely detect HF at baseline and during follow-up among all of the participants, and deal with the missing data and loss to follow-up such as emigrants?
R. Dear reviewer, we improved the manuscript as suggested. In particular, data were derived from the Cardiac Interventional Registry implemented at our hospital; vital status and dates of death were obtained for residents in Puglia by using regional Health Information System and AF/ HF were defined following the European Society of Cardiology guidelines (page 5 ;row 8). We have no missing data and we included only patients resident in Puglia.

Comment on R to Major i).
1. Thank you for your response. It seems to be hard to understand the background of the study population only from the sentence "the Cardiac Interventional Registry implemented at your hospital." Could the authors cite the profile paper of this registry at the authors' hospital? If there is no profile paper, I would like the authors to explain from when until when this registry was conducted and what patients were registered in this registry in the manuscript.

R. Dear Reviewer, in our Hospital all patients who underwent Cardiac Interventional procedures are usually inserted in this Registry. We have been collecting data from 2009 and we decided to analyze data in a 10-year period from January 2009 to June 2019.
We modified the text as suggested (page 5; rows 6-7)

2. If it is applicable, I would like the authors to clearly in the manuscript that AF in this study indicates clinical AF in the ESC guideline (not including AHRE nor subclinical AF), and all cases of AF were diagnosed by ECG at the registration.
R. Dear Reviewer, as suggested we improved our manuscript (page 5; rows 9-11)

3. I suggest the authors explain the definition of drug-refractory AF in this study. For example, the authors defined patients who did not respond to the treatment after using at least X (one, two, three) types of AAD for Y months and more as drug-refractory AF, and so on.
R. Dear Reviewer, as suggested we improved our manuscript (page 5; rows 9-11)

4. I would like the authors to explain in the manuscript how the authors detecteach HF (history of HF at the baseline and new onset of HF during the follow-up). In particular,

for the new onset of HF during the follow-up, I wonder if the authors could specify what algorithm the authors followed and what examination (type of examination and cut-off) the authors used to diagnose the new onset of HF.

R. Dear Reviewer, as requested we clarified the HF diagnosis. In particular, were ported in the text that HF was defined as a clinical condition that required hospitalization according to the ESC guidelines (page 5, rows 11-13)

5. It would be great if the authors could present a flow chart in the manuscript that showed the inclusion and exclusion criteria and the number of the study population.

R. Dear Reviewer, we reported in the text that we included all patients that performed AF ablation procedures in our Center between January 2009 and June 2019. The number of patients was 1260.
This was the only inclusion criteria; no patients were excluded.

ii) p5, line 17- : The authors stated, "data on long-term risk after catheter ablation of AF are lacking." However, several studies have reported the long-term (assumed median/mean several-year follow-up period similar to this study) mortality of patients ablated for atrial fibrillation, with or without HF.
Although these previous studies did not show expected mortality in the general population and SMR in the articles probably due to the different purpose of study from this study, literature-reviews of them are more informative. **To the best of my knowledge, there have been studies that examined the long-term mortality of patients ablated for atrial fibrillation (Saglietto et al., 2020. doi: 10.1111/jce.14429., Samuel et al., 2020. doi: 10.1093/europace/euaa036., Srivatsa et al., 2018. doi: 10.1161/CIRCEP.117.005739., Jarman et al., 2017. doi: 10.2147/POR.S134777., Friberg et al., 2016. doi: 10.1093/eurheartj/ehw087., Nademanee et al., 2015. doi: 10.1016/j.hrthm.2014.09.049., and Bunch et al., 2011. doi: 10.1111/j.1540-8167.2011.02035.x.). There have also been studies that reported the long-term mortality of patients ablated for atrial fibrillation with HF (Marrouche et al., 2018. doi: 10.1056/NEJMoa1707855. , Luigi et al., 2016. doi: 10.1161/CIRCULATIONAHA.115.019406., and Bunch et al., 2015. doi: 10.1111/jce.12602.).**
R. Dear Reviewer, we agree with you regarding the sentence. The aim of this study **is to compare mortality after catheter ablation of AF compared to general population.**
As you suggested, we modified the sentence reporting :"Although AF is significantly associated with mortality and morbidity, data on long-term risk after catheter ablation of AF compared with the general populationis not well characterized and the dynamic of this relative risk is uncertain in terms patient's age and underlying risk profile"
Comment on R to Major ii). Than kyou for modifying the sentence. To make the sentence more specific and more concise, how would you like to revise the sentence as follows?
from
"Although AF issignificantlyassociated with mortality and morbidity, …, especially, presence or occurrence of HF." (pages 4-5, lines 56-60 and 1-6)
to
"Although data on long-termrisksaftercatheterablation of AF with or without HF hasbeenidentified (citation XXX), thosecompared with the general population are notwellcharacterized".

R. Dear Reviewer, as suggested we modified the sentence (page 4, last paragraph)

iii) p5, line 59: The authors stated, "The expected numbers of deaths were derived using mortality rates from the general population of Puglia Region..". In previous studies (Friberg L, et al. 2007. doi:10.1093/eurheartj/ehm308., Potpara, et al.,

2010. doi: 10.2298/vsp1002132p., Olsson, et al., 2013. doi: 10.1016/j.ijcard.2013.10.028., Fored, et al., 2008. doi: 10.1093/europace/eun118.), it seems typical to use national data as the general population for calculating the SMR, probably because they thought that the expected number of deaths would be more accurate among a larger population. The use of only the residents of Puglia Region **as the general population may have limited the generalizability of the results of this study. Was there any specific reason why the author used such an approach?**

VERSION 3 – REVIEW

REVIEWER	タカダ, ミドリ Osaka Center for Cancer and Cardiovascular Disease Prevention
REVIEW RETURNED	12-Mar-2022

GENERAL COMMENTS	Minor point Comment on R to Minor x). Thank you for your response. I apologize if I am wrong, but I don't think there is any need to leave the following text in the manuscript because the authors did not show HRs. “Cox proportional-hazards model was used to estimate Hazard Ratios (HRs) with 95% confidence intervals (CI).”

VERSION 3 – AUTHOR RESPONSE

Response to the Reviewer 2:

We are very grateful to the Editor for his/her attention and helpful comments to our manuscript, which helped to improve our work considerably.

Minor point
Comment on R to Minor x). Thank you for your response.
I apologize if I am wrong, but I don't think there is any need to leave the following text in the manuscript because the authors did not show HRs.
“Cox proportional-hazards model was used to estimate Hazard Ratios (HRs) with 95% confidence intervals (CI).”

Dear reviewer, in the results paragraph we reported the data “History of HF had a crude HR of 4.60 (95%CI 3.00-7.08; p<0.001) with an age- and sex-adjusted value of 3.06 (1.97-4.76; p<0.001)” (page 7, rows 1-2).